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DR. REDDY"S LABORATORIES, INC.
200 SOMERSET CORPORATE BLVD
SEVENTH FLOOR
BRIDGEWATER, NJ 08807-2862

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CHANG, CELIA C

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MANNE SATYANARAYANA REDDY, SAJJA ESWARAIAH, MATHAD VIJAYAVITTHAL THIPPANNACHAR, ELATI RAVIRAMA CHANDRASHEKAR, and PODICHETTY ANIL KUMAR

Appeal 2009-002678
Application 10/816,798
Technology Center 1600

Decided: August 10, 2009

Before TONI R. SCHEINER, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a crystalline form of Donepezil hydrochloride and a method of preparing it. The Examiner has rejected the claims as anticipated and obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

The Specification discloses that "Donepezil hydrochloride is a selective inhibitor of acetyl cholinesterase and is the first promising agent with this mode of action for the treatment of mild to moderate dementia of [the] Alzheimer's type" (Spec. 1-2). The Specification states that previous patents disclosed crystalline forms I through V of Donepezil hydrochloride (*id.* at 2). The Specification discloses a "crystalline form-VI of Donepezil hydrochloride that is specified by the peaks appearing in the powder X-ray diffraction pattern and infrared absorption spectra in potassium bromide" (*id.* at 3).

Claims 2-6 and 8-12 are on appeal. Claim 2 is representative and reads as follows:

Claim 2: Crystalline form VI of Donepezil hydrochloride having an X-ray powder diffraction pattern substantially as depicted in Figure 1.

The claims stand rejected as follows:[1]

- claims 2-6 under 35 U.S.C. § 102(b) in view of Imai[2]; and
- claims 2-6 and 8-12 under 35 U.S.C. § 103(a) in view of Imai, Doelker[3], Wikipedia[4], Davidovich[5], or U.S. Pharmacopia[6].

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[1] Appellants also argue that claims 8-12 were improperly objected to under 37 C.F.R. § 1.75(c) for being in improper dependent form (Appeal Br. 3). However, an Examiner's objection to the form of the claims is not subject to review by appeal (*see* MPEP § 1002.02(c)(4)).
[2] Imai et al., US 5,985,864, Nov. 16, 1999.
[3] Doelker, *Crystalline modification in polymorphic transformations during galenical operations*, 60 ANN. PHARM. FR. 161-176 (2002) (English translation of record, p. 1-36).

ANTICIPATION

Issue

The Examiner has rejected 2-6 under 35 U.S.C. § 102(b) as being anticipated by Imai (Answer 3). The Examiner finds that "donepezil hydrochloride crystals having substantially X-ray powder diffraction as depicted in figure 1 is anticipated by figure 3 product of Imai" (*id.*).

Appellants contend that the X-ray powder diffraction (XRPD) pattern "for *Imai's* crystalline form III of donepezil hydrochloride … is substantially different than the XRPD pattern for crystalline form VI … of the instant application" (Appeal Br. 3).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's finding that Imai's crystalline form III is the same as instantly claimed form VI of Donepezil hydrochloride?

Findings of Fact

1. Imai discloses that "novel polymorphs of Donepezil hydrochloride (I) to (IV) and (V) can be produced and have an excellent stability" (Imai, col. 1, ll. 56-58).

2. Imai discloses that the melting points of the polymorphs are as follows: polymorph (I): 225-226°C (decomposition), polymorph (II): 224-226°C (decomposition), polymorph (III): 229-231°C (decomposition),

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[4] Wikipedia, Polymorphism in pharmaceuticals, http://en.wikipedia.org/wiki/Polymorphism (crystallography), downloaded July 26, 2006.
[5] Davidovich et al., *Detection of Polymorphism by Powder X-Ray Diffraction: Interference by Preferred Orientation*, 7 AM. PHARM. REVIEW 10, 12, 14, 16, 100 (2004).
[6] US Pharmacopia #23, National formulary #18, pp. 1843-1844 (1995).

polymorph (IV): 226-228°C (decomposition), polymorph (V): 218-220°C (decomposition). (*Id.* at col. 7, ll. 7-20.)

3. The Specification discloses that the "[m]elting point of the novel crystalline form VI of Donepezil hydrochloride … is 222-225°C (decomposition)" (Spec. 8).

4. In one example, Imai discloses that polymorph III was prepared as follows:

> 59 g of Donepezil was dissolved in 590 ml of ethanol. Under cooling in a bath containing ice water, 17.8 g of concentrated hydrochloric acid and 885 ml of diisopropyl ether were added successively. After stirring over night at room temperature, filtration of the crystals and drying at 55 °C. for 22 hours afforded 62 g of the [polymorph III].

(Imai, col. 15, ll. 47-56.)

5. In another example, Imai discloses that polymorph III was prepared as follows:

> 10 g of Donepezil was dissolved in 100 ml of ethanol under heating. Under stirring, a mixture of 3.1 g of concentrated hydrochloric acid and 28 ml of ethanol and then 150 ml of diisopropyl ether were added successively. Stirring was continued for 1 hour from the separation of crystals. Filtration of the crystals and drying at room temperature afforded 9.86 g of the [polymorph III].

(*Id.* at col. 16, ll. 33-44.)

6. The Specification teaches that form VI Donepezil hydrochloride was made as follows:

> Donepezil free base (10 grams), was dissolved in methanol (50 ml) at a temperature of 60-65°C along with stirring till a clear solution was obtained. The reaction mass was allowed to cool to a temperature of 25-35°C along with stirring. Isopropyl ether containing 7.5% of dissolved HCl (20.4 ml, correspond to 1.1 equivalent) was added to the reaction mass at 25 to 35°C for

> 10-15min. Isopropyl ether (80 ml) was added further to reaction mass and stirred for 2.0 hours. The obtained crystalline solid material was filtered, washed … and dried … to afford a novel crystalline form VI of Donepezil hydrochloride (9.0[ ]gms).

(Spec. 8-9.)

7. Imai discloses that Figure 3 is a "powder X-ray diffraction pattern of the polymorph III" (Imai, col. 11, ll. 49-50).

8. Imai lists the diffraction angles and relative intensities of the peaks in the polymorph III X-ray powder diffraction pattern (*id.* at col. 3, ll. 33-57).

9. The Specification discloses that Figure 1 is an "X-ray powder diffractogram of novel crystalline Form (VI) of Donepezil hydrochloride" (Spec. 4).

10. The Specification lists the diffraction angles and relative intensities of the peaks in the crystalline form VI X-ray powder diffraction pattern (Spec. 6-7).

11. The X-ray powder diffraction patterns of polymorph III of Imai and form VI of the instant Specification include peaks with different diffraction angles and intensities.

Principles of Law

"[T]he examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art" before the burden is shifted to Applicants to disprove the inherency. *Ex parte Skinner*, 2 USPQ2d 1788, 1789 (BPAI 1986).

Analysis

Claims 2-6 are directed to crystalline form VI of Donepezil hydrochloride. Appellants argue that the "XRPD pattern for *Imai's* crystalline form III of donepezil hydrochloride, shown in Figure 3 of *Imai*, is substantially different than the XRPD pattern for crystalline form VI depicted in Figure 1 of the instant application" (Appeal Br. 3-4). Appellants further argue that "the *Imai* polymorph has a melting point of 229-231°C …, whereas the melting point of crystalline form VI is 222-225°C" (*id.* at 4).

The Examiner finds, however, that "a side by side comparison of the instant pattern and the prior art pattern showed *substantial* similarity" (Answer 5). The Examiner cites Bernstein[7] as disclosing that powder diffraction sample preparation processes "'can lead to variations and inconsistencies among measurements …'" (Answer 5) and that "in an extreme case, as depicted by Berstein [sic] p. 118, very substantial suppression of peaks from a single crystal x-ray can occurred [sic] in the 'powdered' x-ray pattern" (*id.*). The Examiner finds that "if one peak is the same it could be the same crystal" (*id.* at 6).

Appellants' arguments are persuasive. Imai discloses crystalline form III of Donepezil hydrochloride. A comparison of the peaks in the X-ray diffraction patterns for Imai's form III and the instantly claimed form VI shows some similarities, but also shows clearly identifiable differences in the diffraction angles and relative intensities of the peaks.

Bernstein, as the Examiner points out, states that the same compound may yield varying diffraction patterns depending on sample preparation, but

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[7] Bernstein, *Polymorphism in Molecular Crystals*, pp. 115-118, Clarendon Press, Oxford (2002).

the Examiner has pointed to no evidence that supports a finding that sample preparation, rather than differences in crystal structure, accounts for all of the differences between Imai's and the Specification's diffraction patterns. On the contrary, the evidence supports Appellant's position that form VI is a different crystalline form than Imai's form III: Imai discloses that form III has a different melting point from that of form VI, and Imai's form III was made by a different process than that used to make form IV.

Given the differences in powder X-ray diffraction pattern, melting point, and crystallization method, the Examiner has not adequately shown that one of skill in the art would reasonably conclude that form III of Imai is the instantly claimed form VI of Donepezil hydrochloride. Thus, the rejection of claim 2 as being anticipated by Imai is reversed. The rejection of claims 3-6, which depend from claim 2, is reversed for the same reason.

OBVIOUSNESS

Issue

The Examiner has rejected claims 2-6 and 8-12 under 35 U.S.C. § 103(a) as being obvious in view of Imai and one of Doelker, Wikipedia, Davidovich, or U.S. Pharmacopia (Answer 4). The Examiner relies on Imai as discussed above, and concludes that it put the skilled artisan in possession of the claimed invention because "the prior art disclosed the same pure compounds … and its multiple crystalline forms" (Answer 4). The Examiner finds that Doelker, Wikipedia, Davidovich, and U.S. Pharmacopia show that "variation is expected and variation, unless supported by factual comparison, does not support new form but obvious variation of the old form" (*id.* at 5).

Appellants contend that the Examiner erred in finding that the cited references suggest "the particular form VI of donepezil hydrochloride" of claim 2 (Appeal Br. 6).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the cited references suggest crystalline form VI Donepezil hydrochloride?

Principles of Law

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citation omitted).

Analysis

As discussed above, the Examiner has not established that Imai discloses form VI Donepezil hydrochloride. The other references cited by the Examiner disclose that many pharmaceutical compounds exhibit polymorphism and can exist as more than one crystalline form. However, the Examiner has pointed to no disclosures in the prior art that support a conclusion that the cited references would have suggested the specific crystal form of Donepezil hydrochloride that is claimed. Thus, the rejection of claim 2 as being obvious in view of the cited references is reversed. The rejection of claims 3-6 and 8-12, which depend from claim 2, is reversed for the same reason.

CONCLUSIONS OF LAW

The evidence of record does not support the Examiner's finding that Imai discloses crystalline form VI Donepezil hydrochloride. The evidence of record also does not support the Examiner's conclusion that the cited references would have suggested crystalline form VI Donepezil hydrochloride.

SUMMARY

We reverse the rejection of claims 2-6 under 35 U.S.C. § 102(b) in view of Imai, and the rejection of claims 2-6 and 8-12 under 35 U.S.C. § 103(a) in view of the cited references.

REVERSED

cdc

DR. REDDY"S LABORATORIES, INC.
200 SOMERSET CORPORATE BLVD
SEVENTH FLOOR
BRIDGEWATER NJ 08807-2862